REMARKS

Claims 15-29 are pending and under examination in the above-identified application. Claims 22 and 29 have been amended above to correct informalities. Support for the amendment can be found throughout the application and in the claims as filed. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the Office Action mailed May 14, 2004, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 112

Claims 15-19 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description for the immobilization of a target sequence on a solid phase. The Office acknowledges that the specification provides support for the claimed immobilized target but further alleges that the claimed method of hybridizing an immobilized target with a primer having an adapter sequence and subsequently contacting the adapter sequence with an array of microspheres having a capture probe is not described in the specification. In this regard, it appears that because one embodiment of target nucleic acid immobilization is exemplified using an adapter sequence and capture probe configuration, the Office concludes that the use of an adapter sequence in connection with a primer that hybridizes to the immobilized target sequence is precluded despite support for this latter element in the application and claims as filed.

Adequate written description of a claimed invention is satisfied when applicant conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (the written description requirement is satisfied where a person of ordinary skill in the art would recognize that applicant possessed what is now claimed); *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed. Cir. 2002) (the specification must adequately describe the claimed invention so that one skilled in the art can recognize what is claimed).

Applicant submits that the application satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, sufficient for a person of ordinary skill in the art to recognize that

Applicant was in possession of the claimed invention at the time the application was filed. Claim 29 is directed to a method of detecting a target nucleic acid sequence. The method includes hybridizing a first primer having an adapter sequence to a first portion of a target sequence immobilized on a solid phase surface. The application describes both the immobilization of a target sequence and the hybridization of primer having an adapter sequence.

The Office concedes that the specification provides support for the newly claimed immobilized target. Further, the claims pending prior to Applicant's amendment also were supported in the application as filed. Applicant submits that the addition of an element does not render a previously described element unsupported. More specifically, amending the claims to recite that the target sequences are immobilized on a solid phase surface does not render claim elements related to primer hybridization or contacting the adapter sequence with an array as then being unsupported. Moreover, Applicant showed that support for the element to immobilization of a target sequence could be found in the application at, for example, page 69, lines 22-26, and in the last paragraph of page 79, which the Office has acknowledged. Because the claim prior to amendment was supported and because the newly recited element is supported in the application, the description in the application is sufficient to satisfy the written description requirement of the first paragraph of § 112.

Moreover, the application adequately describes the previously recited elements including, for example, both the immobilization of a target sequence and a primer having an adapter sequence sufficient to satisfy the written description requirement of § 112, first paragraph. In this regard, the application describes numerous assay configurations for probes, primers and target sequences, including detection in both solid phase and solution phase formats. The various configurations include any combination of the probes, primers or target sequences being immobilized to a solid phase surface. For example, the application describes:

> The hybridization complex can comprise the capture probe, a capture extender probe, and the target sequence. <u>In addition</u>, the target sequence may comprise exogeneous adapter sequences.

Application at page 7, lines 4-6 (emphasis added).

The application further describes:

> As will be appreciated by those in the art, the systems of the invention may take on a large number of different configurations. In general, there are three types of systems that can be used: (1) "non-sandwich" systems (also referred to herein as "direct" detection) in which the target sequence itself is labeled with detectable labels (again, either because the primers comprise labels or due to the incorporation of labels into the newly synthesized strand); (2) systems in which label probes directly bind to the target sequences; and (3) systems in which label probes are indirectly bound to the target sequences, for example through the use of amplifier probes.
>
> The anchoring of the target sequence to the bead is done through the use of capture probes and optionally either capture extender probes (sometimes referred to as "adapter sequences" herein). When only capture probes are utilized, it is necessary to have unique capture probes for each target sequence; that is, the surface must be customized to contain unique capture probes; e.g. each bead comprises a different capture probe. Alternatively, capture extender probes may be used, that allow a "universal" surface, i.e. a surface containing a single type of capture probe that can be used to detect any target sequence. "Capture extender" probes have a first portion that will hybridize to all or part of the capture probe, and a second portion that will hybridize to a first portion of the target sequence. This then allows the generation of customized soluble probes, which as will be appreciated by those in the art is generally simpler and less costly. <u>As shown herein, two capture extender probes may be used.</u> This has generally been done to stabilize assay complexes for example when the target sequence is large, or when large amplifier probes (particularly branched or dendrimer amplifier probes) are used.

Application at page 50, lines 14-33 (emphasis added).

Additionally, the application also describes, for example, the inclusion of adapter sequences into one or more primers. For example, the application describes that a set of four different extension primers can be used for genotyping, and that each primer will have:

> [A] portion that will hybridize to the target sequence, a different readout base and each with a different adapter sequence of 15-40 bases, as is more fully outlined below.

Application at page 61, lines 25-28 (emphasis added). The adapter sequences are hybridized to an array containing probes complementary to the different adapter sequences (page 61, lines 28-29).

Further, the application also expressly describes solid phase assay formats beginning at, for example, page 62, line 5, where the extension primer also can be used as the attachment to microspheres.

> Alternatively, the reaction may be done on a surface by capturing the target sequence and then running the SBE reaction , in a sandwich type format schematically depicted in Figure 9A. In this embodiment, the capture probe hybridizes to a first domain of the target sequence (which can be endogeneous or an exogeneous adapter sequence added during an amplification reaction), and the extension primer hybridizes to a second target domain. . . . Furthermore, . . . capture extender probes can be used to attach the target sequence to the bead. In this embodiment, the hybridization complex comprises the capture probe, the target sequence and the adapter sequence. Similarly, the capture probe itself can be used as the extension probe. . . . In addition , as outlined herein , the target sequence may be directly attached to the array; the extension primer hybridizes to it and the reaction proceeds. . . . Either before or after extension of the extension probe, a ligation step may be used to attach the capture and extension probes together for stability. These are further described below as combination assays.

Application at page 62, lines 5-31 (emphasis added). Beginning at page 75, line 2, the application exemplifies numerous combination assays employing target sequence immobilization and primer capture using adapter sequences or other capture probe methods. The application expressly describes using the various combinations taught throughout the application when it states:

> It is also possible to combine two or more of these techniques to do genotyping, quantification, detection of sequences, etc.

Application at page 75, lines 3-4. Further, page 79, lines 15-20, exemplify the interchangeability and combination of any of the formats and configurations described throughout the application when it teaches:

> As will be appreciated by those in the art, while generally described as a solid phase assay, this reaction may also be done in solution; this is similar to the solution-based SBE reactions, wherein the detection sequence serves as the extension primer. This assay also may be performed with an extension primer/adaptor oligonucleotide as described for solution-based SBE assays. It should be noted that the arrays used to detect the invasive cleavage/extension reactions may be of any type including, but not limited to, spotted and printed arrays, photolithographic arrays, and bead arrays.

Id. (emphasis added).

Furthermore, the newly recited element of target sequences immobilized on a solid phase surface is supported in the specification, for example, at page 69, lines 22-26 and at the last paragraph of page 79 as set forth previously on the record. Although Applicant agrees with the assertion that "the immobilized target taught by the specification encompasses immobilization via hybridization to capture probes" at page 69, lines 22-26 (see page 3, lines 21-22 of the Office action mailed May 14, 2004), Applicant respectfully submits that it is improper for the Office to limit the teachings of the specification to this particular embodiment. The last paragraph of page 79 teaches:

> In a preferred embodiment, OLA and SBE are combined, as is sometimes referred to as "Genetic Bit" analysis and described in Nikforov et al., Nucleic Acid Res. 22:4167 (1994), hereby expressly incorporated by reference. In this embodiment, the two ligation probes do not hybridize adjacently; rather, they are separated by one or more bases. The addition of dNTPs and a polymerase, in addition to the ligation probes and the ligase, results in an extended, ligated probe. As for SBE, the dNTPs may carry different labels, or separate reactions can be run, if the SBE portion of the reaction is used for genotyping. Alternatively, if the ligation portion of the reaction is used for genotyping, either no extension occurs due to mismatch of the 3' base (such that the polymerase will not extend it), or no ligation occurs due to mismatch of the 5' base. As will be appreciated by those in the art, the reaction products are assayed using microsphere arrays. Again, as outlined herein, the assays may be solution based assays, with the ligated, extended probes being added to a microsphere array, **or solid-phase assays**. In addition, the unextended, unligated primers may be removed prior to detection as needed, as is outlined herein. **Furthermore, adapter sequences may also be used as outlined herein for OLA**.

Id. (emphasis added).

As set forth in the passage above, Applicant was in possession of an assay in which target sequences are immobilized on a solid phase surface. In this regard, the assertion that "the assays may be solution based assays, with the ligated, extended probes being added to a microsphere array, or solid-phase assays," indicates that Applicant was in possession of an assay utilizing array detection of ligated extended probes generated either in solution or on solid phase, as claimed. Furthermore, the above passage, by teaching that adapter sequences can be used as outlined throughout the specification for OLA, demonstrates that Applicant was in possession of the claimed method in which a primer, having, an adapter sequence, is hybridized to the

immobilized target and extended and ligated, as claimed. In view of the teachings throughout the specification, such as those passages set forth above, the Office's conclusion that the use of an adapter sequence in connection with a primer that hybridizes to the immobilized target sequence is precluded merely because one embodiment of target nucleic acid immobilization using an adapter sequence and capture probe configuration is exemplified on page 69, lines 22-26, is unsupported.

In light of the numerous teachings throughout the application that all combinations of methods are included within the scope of the invention and in light of numerous descriptions that either or both the target sequence and the primer can be immobilized to a solid phase surface using, for example, adapter sequences, Applicant maintains that the application provides sufficient written description to convey with reasonable clarity that Applicant was in possession of the claimed invention at the time the application was filed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 29 and 15-28 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite allegedly because the term "said nucleic acid sequence" in claim 29 lacks proper antecedent support and allegedly because it is unclear whether the detection of the nucleic acid detects the target nucleic acid as claimed.

Applicant submits that claim 29 is clear as written and provides proper antecedent basis for the objected term. Step (a) of claim 29 recites hybridization of a first primer to "a target nucleic acid." The reference to "said target sequence" in the subsequent wherein clause follows the initial use of the term "a target nucleic acid" and therefore has proper antecedent support. Further, step (f) has been amended to include the term "target" when used in reference to the detected nucleic acid. Accordingly, the detecting step (f) refers back, and detects, the target nucleic acid sequence recited in the preamble.

Claims 22-28 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite allegedly because the claim is directed to simultaneously detecting at least sixteen target nucleic acid sequences but the method steps allegedly do not accomplish this claimed result.

Applicant submits that claim 22 is clear and definite as filed because it recites hybridizing at least sixteen pairs of primers to at least sixteen target sequences. However, to further prosecution, Applicant has amended claim 22 to recite the hybridization of at least sixteen second primers of the claimed sixteen pairs of primers and the detection of at least sixteen modified primers which indicate the presence of at least sixteen target nucleic acid sequences. Each method step tracks the language of the preamble and the detection step recites detecting the presence of at least sixteen target nucleic acid sequences. Accordingly, this ground of rejection is moot and withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 29, 15-17, 19-20, 22-24 and 26-27 remain rejected under 35 U.S.C. § 103(a) as obvious over Macevicz, U.S. Patent No. 6,280,935, in view of Ullman et al., U.S. Patent No. 5,185,243. Claims 18 and 25 similarly remain rejected under 35 U.S.C. § 103(a) as obvious over Macevicz in view of Ullman et al. and further in view of Walt et al., U.S. Patent No. 6,327,410. Further, claims 29 and 15-28 also remain rejected under 35 U.S.C. § 103(a) as obvious over Barany et al., U.S. Patent No. 6,027,889, in view of Ullman et al. and Walt et al., U.S. Patent No. 6,023,540. The Office maintains each ground of rejection allegedly because the element directed to target sequences immobilized on a solid phase surface lacks written description. In light of this assertion, the Office appears to assess patentability of the claims based on the absence of the rejected term.

Applicant respectfully reminds the Office that adequate written description under the first paragraph of 35 U.S.C. § 112, is a separate statutory requirement from an obviousness inquiry under § 103(a). The Office should evaluate patentability of the claims as written and is not at liberty to omit terms merely because they are in issue under an independent statutory requirement. Therefore, Applicant maintains its arguments of record and reiterates that none of the cited combinations of references suggest or render obvious the invention as claimed. Moreover, and as described previously, the invention as claimed is sufficiently described in the application as filed to satisfy the written description requirement of § 112, first paragraph. Accordingly, these grounds of rejection are moot and withdrawal is respectfully requested.

Claims 29, 15-17, 19-20, 22-24 and 26-27 stand rejected under 35 U.S.C. § 103(a) as obvious over Macevicz in view of Ullman et al. and Collins et al.. The Office alleges that Macevicz describes a method of detecting a target nucleic acid wherein a first primer having an adapter sequence and a second primer is hybridized to a target sequence and ligated to form a modified primer. The modified primer is contacted with an array having discrete sites and a population of microspheres having a capture probe and detected. The Office concedes that Macevicz does not describe that the first and second portions of the target sequences are non-adjacent and extending either the first or second primer toward the other. Ullman et al. is alleged to describe a similar method wherein the extension of non-adjacent primers facilitates diagnostic detection. The Office further concedes that both Macevicz and Ullman et al. do not describe target sequence immobilization on a solid phase surface but alleges that one skilled in the art would have been motivated to include such a step because Collins et al. describes doing so for the benefit of removing non-specific material from the sample, concentrating the target for detection and greater purification of detectable target. Therefore, the Office concludes that it would have been obvious to one of ordinary skill in the art to apply the target immobilization of Collins et al. to the target detection of Macevicz and Ullman et al. for the expected benefit of removal of non-specific material from the sample, concentration of the target for detection and greater purity of detectable product.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). Further, establishing that the prior art would have suggested the claimed invention requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Id.* at 1124-25 (*quoting C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device).

In the pending Office Action, the purported showing for a suggestion to combine fails to point to a suggestion, teaching or motivation in the cited art of the desirability of making the

specific modification, in particular, immobilization of both a target sequence on a solid phase surface and a modified primer on a second solid phase surface such as the claimed microspheres, that was made by the inventor. In this regard, none of the cited art suggest a desirability for changes or improvements over that which is described by each respective inventor. For example, Macevicz describes that his invention "overcomes a key deficiency of current methods of tagging or labeling molecules with oligonucleotides" and that "the problem of incorrect sorting because of mismatch duplexes . . . is eliminated." Col. 5, lines 36-45. Therefore, Macevicz describes satisfactory results with no suggestion, teaching or motivation to include that which was discovered and claimed by the Applicant. Moreover, Macevicz reports satisfaction in his method even in the absence of just one immobilization step. Rather, Macevicz reports that solid phase supports are applicable to automate his method for large scale processes when he describes:

> When used in combination with solid phase supports, such as microscopic beads, my invention provides a readily automated system for manipulating and sorting polynucleotides, particularly useful in large-scale parallel operations, such as large-scale DNA sequencing, wherein many target polynucleotides or many segments of a single target polynucleotide are sequenced and/or analyzed simultaneously.

Col. 5, lines 46-54. Therefore, Macevicz fails to provide any motivation for including immobilization of a target sequence in addition to the use of microspheres because he reports satisfactorily overcoming key deficiencies. Similarly, Ullman et al. also reports satisfactory results in the absence immobilization of a target sequence and a modified primer that overcome previous disadvantages requiring identification of a diagnostic and contiguous sequence. Col. 4, lines 3-12.

Further, Collins et al. also fails to point to a suggestion, teaching or motivation of the desirability of making the claimed immobilization of both a target sequence on a solid phase surface and a modified primer on a second solid phase surface such as the claimed microspheres because the support relied on by the Office is directed to iterative purification and concentration procedures. In this regard, Collins et al. describes:

> Separation of the first support from the first medium removes nonspecifically bound cellular debris attached to the first support. Further binding of the target

> molecule to a second support further concentrates the target for detection and permits further release-capture cycles for greater purification.

Col. 5, lines 19-24 (emphasis added).

Because Collins et al. is directed to the concentration and purification by iterative "release-capture cycles" of a target molecule, the alleged benefit of removing cellular debris, concentrating and purifying a target molecule is inapplicable to the claimed invention. Further, motivation to combine Collins et al. with the methods of Macevicz and Ullman et al. allegedly because the method of Collins et al. concentrates the target for detection is not supported in the description found in Collins et al. because concentrating a target for detection fails to suggest or provide a motivation for immobilization of a target sequence to a solid phase surface followed by binding a modified primer produced therefrom to a second solid phase surface such as a microsphere for subsequent detection. Absent such a suggestion or motivation, Collins et al. cannot provide the required showing necessary to combine the methods of Macevicz and Ullman et al. with a solid phase surface for immobilization of a target sequence as claimed. Therefore, the claimed invention is unobvious over the cited art and withdrawal of this ground of rejection is respectfully requested.

Claims 18 and 25 stand rejected under 35 U.S.C. § 103(a) as obvious over Macevicz in view of Ullman et al. and Collins et al. as applied above and further in view of Walt et al., the '410 patent. Claims 18 and 25 depend from base claims 29 and 22, respectively, and further characterize the claimed array substrate as a fiber optic bundle. Walt et al. is cited for allegedly describing a target detection system containing a fiber optic bundle support.

Because claims 18 and 25 depend from independent claims 29 and 22, respectively, these claims contain all the limitations of the base claim. As set forth previously, neither claim 29 nor claim 22 is rendered obvious over the combination of Macevicz, Ullman et al. and Collins et al.. Further, because Walt et al. is cited for describing a fiber optic bundle support, it does not cure the deficiencies in the primary and secondary references. Accordingly, independent claims 29 and 22 are unobvious over the primary and secondary references and dependent claims 18 and 25 similarly are unobvious over the additional citation to Walt et al.. Withdrawal of this ground of rejection is respectfully requested.

Claims 29 and 15-28 stand rejected under 35 U.S.C. § 103(a) as obvious over Barany et al. in view of Ullman et al., Collins et al. and Walt et al., the `540 patent. The Office alleges that Barany et al. describe a method of detecting a target nucleic acid wherein a first primer having an adapter sequence and a second primer is hybridized to a target sequence and ligated to form a modified primer. The modified primer is contacted with an array having discrete sites containing a capture probe and detection. The Office concedes that Barany et al. do not describe that the first and second portions of the target sequences are non-adjacent nor does Barany et al. describe the use of microspheres. Ullman et al. is alleged to describe a method wherein the extension of non-adjacent primers facilitates diagnostic detection and Walt et al., the `540 patent, is alleged to describe a method using a population of microspheres. The Office further concedes that Barany et al., Ullman et al. and Walt et al. do not describe target sequence immobilization on a solid phase surface but alleges that one skilled in the art would have been motivated to include such a step because Collins et al. describes doing so for the benefit of removing non-specific material from the sample, concentrating the target for detection and greater purification of detectable target. Therefore, the Office concludes that it would have been obvious to one of ordinary skill in the art to apply the target immobilization of Collins et al. to the target detection of Barany et al, Ullman et al. and Walt et al. for the expected benefit of removal of non-specific material from the sample, concentration of the target for detection and greater purity of detectable product.

As with the previous rejection of claims of independent claims 29 and 22 under § 103(a), the substitution of Barany et al. and Walt et al. for Macevicz fails to render the claimed invention unpatentable for similar reasons. In this regard, the purported showing for a suggestion to combine provided in the Office Action fails to point to a suggestion, teaching or motivation in the cited art of the desirability of making the specific modification, in particular, immobilization of both a target sequence on a solid phase surface and a modified primer on a second solid phase surface such as the claimed microspheres, that was made by the inventor. For example, none of the art cited suggest a desirability for changes or improvements over that which is described by each respective inventor.

Further, Collins et al. also fails to point to a suggestion, teaching or motivation of the desirability of making the claimed immobilization of both a target sequence on a solid phase surface and a modified primer on a second solid phase surface such as the claimed microspheres

because the support relied on by the Office is directed to iterative purification and concentration procedures. Because Collins et al. is directed to the concentration and purification by iterative "release-capture cycles" of a target molecule, the alleged benefit is inapplicable to the claimed invention and the motivation to combine is not supported in by Collins et al.. As described previously, concentrating a target for detection fails to suggest or provide a motivation for immobilization of a target sequence to a solid phase surface followed by binding a modified primer to a second solid phase. Absent such a suggestion or motivation, Collins et al. cannot provide the required showing necessary to combine the methods of Barany et al., Ullman et al. and Walt et al. with a solid phase surface for immobilization of a target sequence as claimed. Therefore, the claimed invention is unobvious over the cited art and withdrawal of this ground of rejection is respectfully requested.

Obvious-Type Double Patenting

Claims 15-29 stand provisionally rejected for obvious-type double patenting over certain claims in U.S. Patent No. 6,355,431, and over certain claims in U.S. Patent Application No. 09/425,633. Because these rejections are provisional since the allegedly conflicting claims have not been patented, Applicant respectfully requests to defer responding to these provisional rejections until such time as the claims are allowed and a determination of obviousness as to the allowable subject matter made.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

David A. Gay
Registration No. 39,200

4370 La Jolla Village Drive, Suite 700
San Diego, CA 92122
858.535.9001 DAG:cec
Facsimile: 858.597.1585
Date: November 15, 2004